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Burkholderia cepacia complex outbreaks among non-cystic fibrosis patients in the intensive care units: A review of adult and pediatric literature

Mohammad Abdallah[1], Hassan A. Abdallah[2], Ziad A. Memish[3]

[1]Pharmaceutical Care Services, King Saud Medical City, Riyadh, Saudi Arabia
[2]Prevention and Control of Infection Administration, King Saud Medical City, Riyadh, Saudi Arabia.
[3]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; Infectious Diseases Division, Department of Medicine & Research Department, Prince Mohamed bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia & Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

SUMMARY

Burkholderia cepacia complex (Bcc) is a Gram-negative bacterium commonly found in moist environments and soil. Bcc species are associated with many outbreaks in intensive care units (ICUs). In this review, we describe the sources of Bcc outbreaks among non-cystic fibrosis (CF) patients in various ICUs that include neonatal intensive care units, pediatric intensive care units and adult ICUs. Also we summarize the risk factors and outcome predictors of Bcc infection or colonization in non-CF critically ill patients. Finally, we describe the infection control measures that are used to manage and prevent the spread of Bcc outbreaks.

PubMed was searched from 1 January 1994 and 31 December 2017. We found 30 outbreaks of Bcc among non-cystic fibrosis patients in ICUs; 17 outbreaks occurred in adult ICUs. The source was identified in 22 outbreaks. *B. cepacia* was the most common Bcc species causing outbreaks in ICUs; it was detected in 21 outbreaks. Indwelling central lines, presence of renal failure on hemodialysis, multiple bronchoscopic procedures, and recent abdominal surgery are independently associated with the development of *B. cepacia* bacteremia, while prolonged duration on a mechanical ventilator, a large number of nebulized albuterol therapies delivered, and prescription of beta-lactam, aztreonam, or macrolide-vancomycin antibiotics are risk factors for respiratory tract acquisition of *B. cepacia*. Disease severity and age were the main significant independent predictors of 14-day mortality in adult ventilated non-CF patients with Bcc acquisition.

Bcc species have been linked to many outbreaks in non-CF patients in ICUs. Strict application of infection control standards is critical to limit the emergence and spread of Bcc in ICU settings.

Keywords: *Burkholderia cepacia* complex, Intensive Care Unit, outbreak, infection control, non-cystic fibrosis.

INTRODUCTION

Burkholderia cepacia complex (Bcc) is an aerobic, non-spore forming, catalase-producing, non-lactose-fermenting gram-negative bacterium commonly found in soil and moist environments [1]. It includes at least 21 phenotypically similar but genetically distinct species [2]. Identification of Bcc species using commercial phenotypic assays is complicated, and the inability to easily differentiate the species or the genus from other similar gram-negative bacteria has resulted in significant rates of misidentification [3, 4]. Matrix assisted laser desorption ionization-time of flight mass spectrometry can correctly identify most Bcc

Corresponding author
Mohammad Abdallah
E-mail: mohasulmoha@yahoo.com;
mo.abdullah@ksmc.med.sa

species [5]. Confirmation of identification, speciation, and molecular typing of Bcc isolates should be carried out at a reference laboratory. The genomes of Bcc bacteria are arranged in three circular chromosomal replicons and one to five megaplasmids, ranging from 6.2 up to 8.7 Mbp in size, with a guanine-cytosine content of almost 67%. The large size and distribution of the genomes of Bcc is thought to enhance their flexibility to lose and acquire genes [6]. This vast genetic capacity promotes Bcc versatility in disease and natural biology. Bcc species are opportunistic pathogens in patients with cystic fibrosis (CF). However, its pathogenicity is not limited to CF patients. CF patients are predominantly infected with *B. multivorans* and *B. cenocepacia*, whereas *B. cepacia* is the most prevalent species among non-CF patients [7]. Bcc can survive in fluid environments in healthcare settings, from which it can cause colonization and infection in immunocompromised patients causing respiratory tract, bloodstream and urinary tract infections [8, 9]. Cross-transmission facilitates the spread of Bcc species and several outbreaks in the intensive care units (ICUs) have been reported. Bcc can lead to outbreaks through different sources that include contaminated intravenous medications/fluids, medical devices, or skin disinfectants [10-15]. Bcc associated outbreaks have resulted in recalls of many contaminated products [9, 15, 16]. Identifying the source of Bcc outbreaks can be challenging [8, 17-23]. In this review, we summarize the sources of Bcc outbreaks among non-CF patients in various ICUs that include neonatal intensive care units (NICUs), pediatric intensive care units (PICUs) and adult ICUs. Also, we describe the risk factors and outcome predictors of Bcc infection or colonization in non-CF critically ill patients. Finally, we describe the infection control measures that are used to control and eradicate Bcc outbreaks.

Sources and selection criteria

PubMed was searched using the terms "*Burkholderia*", "outbreak" and "intensive care unit". The search was limited to publications between 1 January 1994 and 31 December 2017. Publications in languages other than English were excluded. Case reports of Bcc infections or colonization in the ICU were excluded. Our search criteria yielded 44 articles; all were screened for relevance to the title of this review. Eight articles were not relevant to the title of this review, while the remaining 36 articles included one case report, one case-control study that investigated risk factors for Bcc bacteremia among non-CF ICU patients, and 34 outbreaks of Bcc in ICUs. Four articles were written in languages other than English (Polish, French and Spanish) while 30 articles met our selection criteria and are described in this review; none of the outbreaks contained CF patients.

RESULTS

Thirty outbreaks of Bcc infection or colonization occurred in non-CF patients in the ICUs. The outbreaks were from all continents except Africa. Seven outbreaks were reported from USA, 4 from India, 3 from France and 2 from Canada. One outbreak was reported from each of the following countries: Argentina, Australia, China, Ecuador, Greece, Israel, Italy, Japan, Malaysia, Oman, Republic of Korea, Saudi Arabia, Spain and Taiwan. Almost half of the outbreaks occurred in adult ICUs (n=17) outbreaks, 10 outbreaks occurred in NICUs whereas 4 outbreaks occurred in the PICU. Three outbreaks were mixed; one occurred in an adult ICU and NICU, and two occurred in a NICU and PICU. The age group of patients (adult ICU, PICU or NICU) was not specified in 2 outbreaks. The source was identified in 22 outbreaks. *B. cepacia* was the most common Bcc species causing outbreaks in the ICUs; it was detected in 21 outbreaks. It is worth mentioning that some laboratories were unable to distinguish species and often Bcc species are mentioned in the literature as *B. cepacia*. In the 21 outbreaks that reported *B. cepacia*, 16 outbreaks performed genotyping to identify Bcc species while genotyping was not performed in 5 outbreaks. Genotyping of Bcc was performed in 25 outbreaks; pulsed-field gel electrophoresis (PFGE) was the most common typing method performed (n=13). Bcc isolates were isolated from blood, respiratory sites, urine, stool, wound, abscess and ascetic fluids. The reported outbreaks varied in terms of duration (from 2 weeks up to 4 years). Treatment of Bcc infections was described only in 9 outbreaks. Definition of infection and/or colonization was mentioned in 15 outbreaks; many outbreaks had different definitions for infection and/or colonization. Bcc related outbreaks among non-CF ICU patients are summarized in Table 1.

Sources of Bcc outbreaks

The source of Bcc outbreak was identified in 22 outbreaks. Contaminated medical products have been associated with many outbreaks. The contamination can be either extrinsic (introduced while the medical product is in use), or intrinsic (that is present when the medical product is received in the hospital). The contamination category of medical products (intrinsic or extrinsic) was not identified in some outbreaks. Intrinsically contaminated medical products that caused Bcc outbreaks included liquid docusate; skin antiseptic that contained 0.5% chlorhexidine gluconate as the active ingredient; IV caffeine citrate; upper surface of capped rubber stoppers of lipid emulsion; alcohol-free mouthwash; ultrasound gel; and moisturizing body cream [9, 15, 11, 28-34, 37, 38]. While extrinsically contaminated medical products that caused Bcc outbreaks included IV fluid bottles of both sodium chloride and 5% dextrose that were used to prepare total parenteral nutrition for neonates; albuterol nebulization solution; Indigo carmine dye; and distilled water used in procedures such as nebulizations, flushing orogastric tubes and humidification of oxygen [10, 25-27, 35, 36]. Other sources of Bcc outbreaks were contaminated upper surface of a rubber stopper of sealed multi-dose amikacin vials; contaminated mechanical ventilator; and contaminated blood gas analyzer [24, 12-14].

Risk factors of Bcc bacteremia and respiratory tract acquisition among non-CF patients

Two studies provided data on risk factors of *B. cepacia* bacteremia among hospitalized non-CF critically ill patients [20, 39]. A case-control study identified the presence of indwelling central lines, presence of renal failure on hemodialysis, multiple bronchoscopic procedures, and recent abdominal surgery as independently associated with the development of *B. cepacia* bacteremia [39]. Respiratory compromise was more severe among cases than controls, as shown by the need for mechanical ventilation, the duration of mechanical ventilation, and subsequent receipt of a tracheostomy. Cases had longer ICU stays preceding the date of *B. cepacia* bacteremia. The presence of percutaneous endoscopic gastrostomy tube was proven to be a protective factor. It is thought that its protective effect is related to its significant role in reducing gastric aspiration, in addition to minimizing the use of nasogastric tubes which limits respiratory colonization which in ventilated patient is a prerequisite for development of pneumonia and Bcc bacteremia. The prolonged use of central lines in the babies was suggested as a significant risk factor in an outbreak of *B. cepacia* septicemia in a NICU [20]. Risk factors of Bcc respiratory tract acquisition in non-CF patients were investigated in two case control studies [23, 27]. Pegues *et al*. found that adult mechanically ventilated patients who had positive growth of *B. cepacia* in the sputum were more likely to be on mechanical ventilation for 2 or more days, or to have been intubated more than once before the detection of first of *B. cepacia* isolate, were significantly more likely to have received a medication through nebulization, and a cephalosporin antimicrobial in the 10 days before the detection of first isolate of *B. cepacia* [23]. Hamill *et al*. identified that prolonged duration on mechanical ventilator, higher number of nebulized albuterol therapy delivered, and prescription of beta-lactam, aztreonam, or macrolide-vancomycin antibiotics are risk factors for respiratory tract acquisition of *B. cepacia* [27].

Outcome predictors

Outcome predictors in non-CF critically ill patients with Bcc acquisition (infection or colonization) were investigated in 2 reports [19, 30]. Outcome predictors were reviewed in an outbreak of Bcc among adult ventilated non-CF patients involving 33 colonized and 13 infected patients [30]. Among many demographic and clinical variables reviewed; disease severity and age were the only significant independent predictors of 14-day mortality (odds ratio: 1.12; 95% confidence interval: 1.02-1.26; and 1.07; 1.01-1.15, respectively); elderly patients and patients with high Simplified Acute Physiology Score (SAPS) II had higher 14-Day mortality. Age, SAPS II score, ceftazidime treatment, co-infections and chronic pulmonary disease were associated with a 28-day and/or in-hospital mortality risk in univariate analysis, but this association was not confirmed by multivariate analysis. Patient mortality at 2 weeks was 28.3% and 34.8% at 4 weeks, while overall in-hospital mortality was 50%. In contrast, the observed mortality rates were 11.5% in the same time-period for all ICU patients and in-hospital mortality was 20.3%. The higher mortality rates seen in patients with Bcc were not much different from

Table 1 - Summary of *Burkholderia* cepacia complex outbreaks that occurred among non-CF patients in the ICUs

Reference	*Location of outbreak*	*Period*	*Setting*	*No. of patients*	*No. of infected patients*	*No. of colonized patients*	*Bcc species identified*	
Siddiqui et al (8)	United States	September 1997 -September 1999	ICU	31, 17 were examined	12 out of 17 examined	5 out of 17 examined	*B. cepacia*	
Marquez et al (9)	United States	February -July 2016	PICU	24	17	7	N/R	
Paul et al (10)	India	January -March 2014	NICU	12	11	1	*B. cepacia*	
Shrivastava et al (11)	India	September -October 2015	NICU	7	7	0	*B. cepacia*	
Loukil et al (12)	France	December 1998 -October 2001	PICU and NICU	32	18	12	*B. cepacia*	
Guo et al (13)	China	June 1- 14, 2015	Adult ICU	4	4	0	*B. cepacia*	
Gravel-Tropper et al (14)	Canada	November 1990 -June 1993	NICU	13	8	5	*B. cepacia*	
Song et al (15)	Republic of Korea	November 2014 - January 2015	NICU	21	0	21	*B. cepacia*	
Katsiari et al (17)	Greece	December 2009 -August 2010	Adult ICU	21	21	0	*B. cenocepacia*	
Kuzumoto et al (18)	Japan	July -October 2010	NICU	6	1	5	N/R	
Liao et al (19)	Taiwan	January 2004 -December 2007.	Adult ICU	95	95	0	*B. cepacia*	
Lee (20)	Malaysia	In 2001 (period was N/R)	NICU	23	23	0	*B. cepacia*	
Graindorge et al (21)	France	March -July 2004	Adult ICU	7	7	0	*B. cenocepacia*	
Manzar et al (22)	Oman	N/R	NICU	4	0	4	*B. cepacia*	
Pegues et al (23)	United States	1 January - 31 December 1994.	Adult ICU	70,of which 30 were mechanically ventilated	N/R	N/R	*B. cepacia*	
Mali et al (24)	India	June 2012 -January 2013	PICU and pediatric ward	76	76	0	N/R	
Reboli et al (25)	United States	February -December 1992	Adult ICU	44, 38 were on mechanical ventilation	16 of the 38 mechanically ventilated were infected	22 of the 38 mechanically ventilated were colonized	*B. cepacia*	
Ramsey et al (26)	United States	January -November 1998	Adult ICU	9	7	2	*B. cepacia*	
Hamill et al (27)	United States	July 1990 – January 1991	Adult ICU	42	15	27	*B. cepacia*	
Doit et al (28)	France	October 2001 -April 2002	NICU and PICU	7	7	0	*B. cepacia*	

	Typing method	*Source of outbreak*	*Sample site*	*Treatment*	*Outcome*
	PCR, PFGE, RAPD, and automated ribotyping	N/R	Respiratory Tract (n = 15)	N/R	N/R
	Rep-PCR	Liquid docusate	Respiratory tract cultures (n = 18), blood (n = 5), urine (n = 4), stool (n = 3)	N/R	N/R
	Not performed	IV fluids	Blood	N/R	9 survived, 2 died
	Not performed	IV caffeine citrate	Blood	MEM + LVX	All survived
	Ribotyping	Ventilators	Tracheal aspirates (n = 28), blood (n = 4)	N/R	N/R
	Not performed	Ventilators	Endotracheal aspirate	SXT + CIP (n = 3), CTZ (n = 1)	3 survived, 1 died
	Ribotyping	Blood gas analyzer	Blood	N/R	All improved clinically
	PFGE	Skin antiseptic (0.5% Chlorhexidine)	Blood	None	All survived
	PFGE	N/R	Blood	N/R	15 survived, 5 died
	PFGE	N/R	Nasal secretion (n = 1), tracheal aspirate (n = 4), blood and urine (n = 1)	N/R	N/R
	PFGE	N/R	Blood	MEM, PTZ, CAZ (number of patients on each antibiotic was N/R)	79 survived, 16 died
	PFGE	N/R	Blood	N/R	21survived, 2 died
	PCR, RELP and PFGE	N/R	Respiratory tract cultures	CAZ + SXT	6 survived, 1 died
	Not performed	N/R	ETT secretions	Only the index case received antibiotic but it was N/R	The index recovered while the outcome of the three remaining cases was N/R
	PFGE	N/R	Sputum	N/R	11 died, 19 survived
	PCR and EMLST	Rubber stopper of amikacin vials	Blood	N/R	42 responded to treatment, 21 died. Outcome was N/R in 13 children
	PCR-ribotying and plasmid analysis	Albuterol nebulization solution	Respiratory tract cultures	N/R	N/R
	PFGE	Albuterol nebulization solution	Sputum	N/R	7 survived, 2 died
	Rep-PCR	Albuterol nebulization solution	Respiratory sites	N/R	N/R
	Ribotyping	Lipid emulsion stoppers	Blood	CAZ (n = 1), CAZ and CIP (n = 6)	All survived

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Reference	*Location of outbreak*	*Period*	*Setting*	*No. of patients*	*No. of infected patients*	*No. of colonized patients*	*Bcc species identified*
Zurita et al (29)	Ecuador	March 2011 -May 2012	Adult ICU	13	3	10	*B. cepacia*
Righi et al (30)	Italy	16-month outbreak period	Adult ICU	46	13	33	N/R
Matrician et al (31)	United States	August 1996 -June 1998	ICU	69	33	36	*B. cepacia*
Abdelfattah et al (32)	Saudi Arabia	January -June 2016	Adult ICU	14	N/R, but 11 patients received treatment for Bcc	N/R, but 3 patients did not receive treatment for Bcc	*B. cepacia*
Nannini et al (33)	Argentina	April -July 2013	Adult ICU and NICU	11	11	0	*B. stabilis*, *B. contaminans*, and *B. ambifaria*
Shaban et al (34)	Australia	March - April 2017	Adult ICU	11	0	11	*B. cenocepacia*
Gravel et al (35)	Canada	August - November 1998	Adult ICU	14	10	4	*B. cepacia*
Antony et al (36)	India	N/R	PICU	3	3	0	*B. cepacia*
Álvarez-Lerma et al (37)	Spain	18 days	Adult ICU	5	5	0	*B. cepacia*
Wiener-Well et al (38)	Israel	July 2010 - August 2010	Adult ICU	4	two were infected while the remaining were N/R as either infected or colonized	N/R	*B. cenocepacia* and *B. stabilis*

CAZ: ceftazidime, CF: cystic fibrosis, CIP: ciprofloxacin, CTX: cefotaxime, CTZ: ceftizoxime, DNA: deoxyribonucleic acid, EMLST: expanded multilocus sequence typing, ETT: endotracheal tube, GEN: gentamicin, ICU: intensive care unit, IV: intravenous, LVX: levofloxacin, MEM: meropenem, MLST: multilocus sequence typing, N/R: not reported, PCR: polymerase chain reaction.

those occurring in patients with any kind of ICU infection. In an outbreak of *B. cepacia* bacteremia involving 95 ICU patients over a 4-years period, patients with more severe disease at the onset of infection and patients with significant underlying disease including underlying malignancy had higher mortality [19]. So, rapid initiation of appropriate antibiotics and full supportive treatment are critical for improving outcomes in patients with Bcc bacteremia.

Infection control measures

The multidrug-resistant Bcc is a common cause of healthcare associated infections in hospitals; it has high transmissibility between patients through direct or indirect contact with contami-

	Typing method	*Source of outbreak*	*Sample site*	*Treatment*	*Outcome*
	MLST	Alcohol-free mouthwash	Tracheal aspirate	Oral SXT alone (n = 5), oral SXT + MEM n = (n = 1), CAZ (n = 3), MEM (n = 1) , patients were not treated (n = 3)	10 survived, 3 died
	RAPD	Alcohol-free mouthwash	N/R	PTZ (n = 15), CAZ (n = 12), SXT (4)	23 survived, 23 died
	PFGE	Alcohol-free mouthwash	Respiratory tract cultures	N/R	Mortality rate for patients with *B cepacia* = 31.2% at hospital A and 47.5% at hospital B, Deaths could be attributed to infection
	PFGE	Ultrasound probe gel	Blood	MEM (n = 5), SXT (n = 2), MEM + SXT (n = 1), MEM + TEC (n = 1), CAZ (n = 2), did not receive treatment (n = 3)	9 survived, 5 died
	DNA sequencing technique	Ultrasound probe gel	Blood	N/R	11 patients died (two adults and one neonate)
	MLST	Ultrasound probe gel	Blood (n = 9), abscess fluid (n = 1), ascetic fluid (n = 1)	None	All cases survived, 7 patients were discharged
	PFGE	Indigo carmine dye	Sputum (n = 7), wound (n = 5), urine (n = 1), blood (n = 1)	N/R	9 survived, 5 died
	Not performed	Distilled water	Blood	Piperacillin (n = 1), CTX (n = 1), CTX and GEN (n = 1)	All recovered
	PFGE	Moisturizing body milk	Blood (n = 3), respiratory site (n = 1), urine (n = 1)	N/R	All survived
	PCR-ribotying	Moisturizing cream	Blood	Two patients received antibiotics but were N/R	Two recovered The outcome of remaining cases was N/R

PFGE: pulsed-field gel electrophoresis, PTZ: piperacillin/tazobactam, RAPD: random amplification polymorphic DNA, Rep-PCR: repetitive extragenic palindromic sequence-based PCR, RFLP: restriction fragment length polymorphism, SXT: trimethoprim-sulphamethoxazole, TEC: teicoplanin.

nated surfaces and exposure to *B. cepacia* in the environment [12, 13]. Improved antibiotic utilization and strict application of infection control standards are critical to limit the emergence and spread of Bcc in the ICU settings [11, 14, 24-28, 36]. Continuous surveillance for this pathogen and rapid initiation of infection control investigation of any clusters of infection and colonization are very important for early detection and resolving outbreaks [10].

Strict infection control measures are critical in preventing acquisition of *B. cepacia* among patients with CF and non-CF [40]. Non-compliance with infection control practices is the main reason for cross-transmission and contributes to the spread of *B. cenocepacia* and *B. cepacia* [26, 33]. Af-

ter reviewing the literature, we believe that strict infection control measures that include contact precautions are pivotal in halting the spread of Bcc outbreaks [8]. If isolating the patients with Bcc is not feasible, cohorting patients in one area can prevent Bcc spread. Other precautions include applying full compliance with hand hygiene, use of disposable gowns and gloves, dedicated medical equipments for the affected patient (*e.g.* thermometer, stethoscope and pulse oximeter) and limit visiting. Intensive education for health care professionals especially nurses and respiratory therapists to review infection control measures are necessary [8, 28]. Getting rid of intrinsically contaminated products is mandatory [9, 11, 15, 29, 31-34, 38]. Finally, ICU cleaning and disinfection have been proven to be necessary to eliminate Bcc outbreaks [12, 13, 17, 35].

CONCLUSIONS

Bcc related infections influence morbidity and mortality among non-CF ICU patients. Bcc species have innate resistance to many antibiotics, which makes a challenge in their treatment. They are known to cause outbreaks in various ICUs. Several sources are identified to cause the outbreaks. Identifying the outbreak source can be challenging; the source can be undetected in many situations despite adequate surveillance and investigation. After discovering the source, removing the source is an essential step to limit the outbreak spread. Strict infection control measures that include contact precautions, educational programs and disinfection are important in eliminating Bcc associated outbreaks.

Conflict of interest
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